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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	16

DATE MAILED: 11/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/531,438	Applicant(s) Gibert et al
	Examiner Portner	Art Unit 1645

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 12, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *42-73* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *42-73* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-41 have been canceled.

New claims 42-73 have been added.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Sequence Letter

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

3. APPLICANT IS GIVEN the time period set for THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Please Note: ~~With the~~ Submission of ~~the~~ a new sequence listing that contains original sequence 2, which was later changed to be SEQ ID No 3 is required. SEQ ID NO 3 has been deleted and a new sequence which differs from original sequence 2, later referred to as SEQ ID No 3 has been submitted. The originally submitted sequence should be added to the sequence listing to place the Application in sequence compliance. Deletion of a sequence for the specification would be New Matter. Omission of a sequence can be added back to the sequence listing. The newly

added SEQ ID NO 3 is not considered to be New Matter as it evidences original descriptive support, but deletion of an original sequence completely from the specification would constitute New Matter.

Objections and Rejections Withdrawn

4. Brief Description of the Drawings has been amended to recite SEQ ID NO 2, designated as being contained in both figure 8A and 8B.

5. Claims 1, 9-11 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 5,874,220, in light of the amendment of the claims.

6. Claims 1-3 and 19 directed to a product of nature, as the nucleic acid is not isolated and purified, in light of the cancellation of the claims.

7. Claims 1-8, 10-11, 14-17, 24, 26-27, 35-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the cancellation of the claims.

8. Claims 1-17,19, 24, 26-37 rejected under 35 U.S.C. 102(b) as being anticipated by Gibert et al (Gene, December 5, 1997), in light of Applicant's perfected foreign priority.

9. Claims 1, 4, 7-8, 9-13,14-17, 24, 26-37 rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al (US Pat. 5,955,368), in light of Applicant's perfected foreign priority.

10. Claim 1 rejected under 35 U.S.C. 102(b) as being anticipated by WO97/37685 (October 16, 1997), in light of Applicant's perfected foreign priority.

11. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Draper et al (US Pat. 5,693,535), in light of the functional limitation recited in the claims.

12. Claim 1 rejected under 35 U.S.C. 102(b) as being anticipated by WO96/30043 (October 3, 1996), in light of the functional limitation recited in the claims.

13. Claim 1 rejected under 35 U.S.C. 102(b) as being anticipated by WO91/18997 (December 12, 1991), in light of the functional limitation recited in the claims.

Rejections Maintained

14. Claims 42-73, as previously applied to claims 1-17, 19, 24, 26-37 are rejected under 35 U.S.C. 112, first paragraph *(written description)*, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (scope).

Priority

15. The instant Application claims priority under 35 U.S.C. 119 (a)-(d) and 365 (b) and 35 U.S.C. 120; the priority has been perfected.

Response to Arguments

16. Applicant's arguments filed August 12, 2002 have been fully considered but they are not persuasive.

17. The rejection of claims 42-73, as previously applied to claims 1-17, 19, 24, 26-37 ~~are rejected~~ under 35 U.S.C. 112, first paragraph *(written description)*, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (scope), is traversed on the grounds that "The rejection of Claims 1-17, 19, 24, 26-37 under 35 U.S.C. 112, first paragraph is obviated by the cancellation of these claims" *and by* stating "The specification defines the terms "portion" and "fragment" on the paragraph bridging pages 4-5 of the present specification.

18. It is the position of the examiner that the specification states "portions" can readily be generated using conventional molecular biological techniques". No written descriptive support could be found for any specific portions that evidence transcriptional promoter activity ~~could be found~~. An invitation to experiment was set forth through the statement "can readily be generated

using conventional molecular biological techniques". This portion does not provide original descriptive support for the now claimed genus of purified nucleic acids that comprise any 50 base pairs or more and transcriptional promoter activity.

No discussion was found with respect to specific "fragments" that would evidence transcriptional promoter activity at pages 4-5 of the instant specification.

19. Applicant directs the examiner to page 4-17 with respect to the definition of the term "hybridizing" to provide written descriptive support for the claimed purified nucleic acid.
20. It is the position of the examiner that while the specification defines various hybridization conditions, both stringent and non-stringent conditions, no purified nucleic acids were disclosed other than SEQ ID NO 3 at page 5, line 15. The narrative found at page 4-17 also defines an invitation to experiment, to locate and to identify additional nucleic acid molecules with the recited function.

21. At page 5, lines 18-24 Applicant describes how to determine transcriptional promoter activity.
22. It is the position of the examiner that the rejection was a lack of written description. A method of isolating a nucleic acid provides guidance on how to make and use, but does not show possession of the instantly claimed genus of purified nucleic acid molecules.

23. The term "toxin" is defined on page 6-7 and asserted to provide written description of the claimed invention.
24. Upon consideration of the disclosure at pages 6-7, various biological characteristics of toxins was found, along with various general suggestions for the detoxification of the toxin, but no written descriptive support for the now claimed genus of purified nucleic acids with transcriptional activity that comprise any portion, any fragment of SEQ ID NO 3, is variant of the Clostridium perfringens beta 2 toxin promoter, or any nucleic acid that will hybridize to the

complementary strain of SEQ ID NO 3 of any size and evidences transcription promoter activity, as well as expression cassettes, vectors, recombinant cells and methods of using all of these products in a method of making a polypeptide that is a transgene in association with the claimed genus of purified nucleic acids could be found. In summary, it is the position of the examiner that the claimed genus of purified nucleic acids that evidence transcriptional promoter activity has not been described, nor has the genus of signal sequences that comprise any portion of SEQ ID NO 4.

The variant nucleic acids and transgenes that comprise only portions, parts or are variants of SEQ ID NO 3, correspond to sequences from other bacterial species, mutated sequences, allelic variants encoding polypeptides from any source. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Allowable Subject Matter

25. Claims limited to SEQ ID NO 3 or SEQ ID NO 4 would be allowable, if the non-described species of invention were removed.

26. A purified Nucleic acid molecule that hybridize under stringent conditions over the full length of SEQ ID NO 3 and evidence transcription promoter activity from Clostridum perfringens could define allowable subject matter.

27. A purified nucleic acid molecule that hybridizes under stringent conditions over the full length of SEQ ID No 4, and encodes a peptide that functions as a secretion signal peptide of Clostridium perfringens, also could define allowable subject matter.

New Grounds of Objection and Rejection

Specification

28. The disclosure is objected to because of the following informalities: The first sentence of the Specification has been amended to define the PCT/Fr98/01999 to have a filing date of September 17, 1999. If this is the case, then priority to the French Application would be more than 1 year, which was filed on September 19, 1997. Clarification of the first sentence of the specification is requested. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

29. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

30. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

31. Claims 56-57, 59, 61, 71-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the transformation and expression of a prokaryotic host cell with a coding sequence for Clostridium perfringens beta toxin 1 or 2 controlled by a prokaryotic transcriptional promoter nucleic acid sequence of SEQ ID No 3 and a signal sequence of SEQ ID NO 4 , does not reasonably provide enablement for the transformation and expression of a coding sequence for Clostridium perfringens beta toxin 1 or 2 controlled by a prokaryotic transcriptional promoter nucleic acid sequence in a eukaryotic cell. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 56-57, 59, 61, 71-73 are directed to a method of producing a polypeptide in any cell, utilizing the prokaryotic promoter of claim 42. While the instant specification has enabled the transformation of prokaryotic cells with the prokaryotic promoter, the instant specification has not described, nor provided guidance for the transformation of any eukaryotic cell with the purified Clostridium nucleic acid of claim 42.

While the transgene coding for a polypeptide, under the control of the nucleic acid of claim 42, could be introduced into a eukaryotic cell, the expressing method step would not be enabled as induction of expression of the prokaryotic promoter in a eukaryotic cell would not predictably function absent specific guidance. No polypeptide would be recovered, as no transgene product would be expressed. The claims directed to the utilization of any cell in a method of producing a polypeptide is not enabled for the full scope of the claims.

32. Claims 43-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 depends from claim 42 and recites the phrase "a portion thereof". Claim 43 does not require the portion to evidence "transcriptional promoter activity", thus broadening the scope invention. This rejection could be obviated by amending the claim to recite --transcriptional promoter activity--.

Claim 44 recites the phrase "a fragment thereof" and depends from claim 42. This phrase lacks antecedent basis in claim 42.

Claim Rejections - 35 U.S.C. § 102

Please Note: The examiner is reading the phrase "variant thereof" to include purified nucleic acids that evidence the recited function of having transcriptional promoter activity, but evidence a variant nucleic acid sequence relative to SEQ ID No 3.

33. Claims 42, 45, 48-49, 50, 54-56, 61-65,66-69, 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Hunter et al (1993, reference of record).

(composition claims) Hunter et al disclose the claimed invention directed to a purified nucleic acid, wherein the nucleic acid encoded for a Clostridium transcriptional promoter variant of SEQ ID NO 3 (chromosomal DNA from Clostridium perfringens comprises a plurality of transcriptional promoters based upon the number of operons contained therein (see page 3958, col. 2, paragraph)).

The reference also discloses an expression cassette and vector that comprise an additional variant transcriptional promoter, the cassette vector designated as pBET7. The cassette vector comprised a transgene, specifically a portion of Clostridium perfringens beta toxin. The expression cassette vector was used to transform a prokaryotic host cell (see page 3959, col. 2, paragraph 1).

(Method claims) A method of producing a polypeptide is disclosed, wherein the method comprised the steps of :

introducing a transgene (Clostridium perfringens beta toxin, heterologous to E.coli) encoding a polypeptide into a host cell (E.coli) under the control of a variant transcriptional promoter in the plasmid expression cassette vector;

expressing said transgene (E.coli cultured at 37 degrees C, with shaking until OD 0.5 at 600 nm);

recovering the polypeptide (periplasmic and cytoplasmic fraction of the cells were prepared to obtain the expressed polypeptide (see page 3959, col. 2, paragraph 1).

Conclusion

34. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

36. Yu et al (US Pat. 5,49,6725) disclose and claims a recombinant host cell (see claims 1-3) that comprises a purified nucleic acid promoter (see Yu et al claim 3), signal sequence (see Yu et al, claim 3) and a transgene coding sequence for the recombinant cell (cellulase structural gene sequence.

37. Miller (US Pat. 5,266,474) disclose the claimed invention which is directed to a purified nucleic acid, that is a variant of SEQ ID No 3, wherein the purified variant nucleic acid has a transcriptional promoter activity (see claims).

38. Topfer et al (US Pat. 6,133,506; effective filing date May 23, 1996) disclose a purified nucleic acid that shares 53.2 % local similarity to SEQ ID NO 3, over 143 nucleotides, and is a variant of the instantly claimed SEQ ID NO 3.

39. Schoner et al (5,192,669)disclose the claimed invention which is directed to a purified nucleic acid, that is a variant of SEQ ID No 3, wherein the purified variant nucleic acid has a transcriptional promoter activity (see Schoner et al, title, abstract, claims).

40. Palva et al (US Pat. 5,529,908) is cited to show promoters and signals for the expression of heterologous polypeptides in bacteria.

41. Natesan (US Pat. 6,015,709) is cited to show transcriptional activators that are variants of the claimed invention.

42. Steinthorsdottir et al (1995) is cited to show a signal sequence and coding sequence containing purified nucleic acid of Clostridium perfringens linked to a transgene as a fusion protein, and expressed in a recombinant host cell.

43. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
November 5, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.: 09/531,438

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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